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Pamidronate treatment of bone fibrous dysplasia in nine children with McCune-Albright syndrome

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McCune-Albright syndrome is a rare genetic disorder consisting of skin and bone dysplasia and peripheral endocrinopathies. Little data have been collected regarding bisphosphonate treatment of bone fibrous dysplasia in paediatric patients with this syndrome. The aim of our study was to investigate the therapeutic efficacy of pamidronate in these patients. Nine patients with moderate to severe forms of bone fibrous dysplasia were treated with pamidronate intravenously (0.5–1 mg/kg/daily for 2–3 d) at 0.5–1-y intervals. Patients were treated over a time period of 0.5–3.5 y. During treatment no spontaneous fracture occurred. Bone pain and gait abnormality due to pain disappeared after 2–3 therapeutic cycles. Cranial asymmetry and limb length discrepancy remained unchanged. Elevated serum alkaline phosphatase and urine hydroxyproline values were reduced by the treatment, demonstrating drug activity at the lesional level. The effectiveness of pamidronate was also seen at the non-lesional level through an increase in bone density. Radiographic and scintigraphic evidence of lesion healing was not attained. Pamidronate treatment can ameliorate the course of bone fibrous dysplasia in children and adolescents with McCune-Albright syndrome. □ *Bone fibrous dysplasia, McCune-Albright syndrome, pamidronate*

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McCune-Albright syndrome (MAS) is a rare, sporadic condition, defined by three main features: skin dysplasia (as cutaneous *café au lait* spots), bone fibrous dysplasia (BFD) and autonomous hyperfunctioning endocrinopathies (1, 2). The syndrome is caused by a postzygotic missense mutation in the gene codifying the alpha-subunit of the Gs protein belonging to the receptor system of most proteic hormones (3). This abnormal Gs protein constitutively activates the adenylatecyclase system, causing autonomous cell proliferation in skin and bones and hormonal hypersecretion involving the gonads, hypophysis, thyroid and adrenal glands (4). Hypophosphatemia due to renal phosphate wasting is one of several endocrine/metabolic disorders associated with MAS (5); its precise prevalence is unknown (5).

BFD in MAS, consisting of osteolytic lacunar areas in long bones and skullcap and sclerosis of the skull base, is due to hyperproliferation of pre-osteoblastic cells (6). Lesions are monostotic or polyostotic and may be asymptomatic or cause pain and spontaneous fractures. They occur mainly in femur, shinbone, ribs and facial bones, and may cause deformity and limb dysmetry. Skull bone involvement may progress towards neurological damage, blindness, deafness and vestibular dysfunction (7). Bone involvement in MAS cannot be distinguished from the more common forms of monostotic and polyostotic fibrous dysplasia (8, 9).

At the moment no satisfactory medical treatment of BFD is known. Therapeutic trials with inhibitors of bone resorption like calcitonin and clodronate have not proven successful (10, 11). Pamidronate, an aminobisphosphonate effective in Paget disease of bone, has been tried in adult patients with BFD, with encouraging preliminary results (12–15). Despite a report showing that bisphosphonates at high doses may induce, in children, metaphyseal mineralization defects (16), favourable preliminary results with no negative side effects in a cohort of paediatric patients have been recently published (17).

The aim of our study was to investigate the efficacy of long-term treatment with intravenous pamidronate in a group of nine children with moderate or severe forms of BFD in MAS.

Subjects and methods

Nine children (7 F, 2M, mean age at the beginning of

Table 1. Main clinical data at diagnosis.

	DPE	CM	NA	LR	CD	DRD	CA	MR	AR
Cases	1	2	3	4	5	6	7	8	9
Sex	F	F	F	F	F	F	F	M	M
Bone dysplasia[a]	++	+++	+++	+	+++	++	+++	+++	++
Sites	C + LB	C + LB	LB	LB	C + LB	LB	C + LB	C + LB	C
Skin dysplasia	+	+	−	+	+	+	+	+	+
Precocious puberty	+	+	+	+	+	+	+	+	+
Cushing syndrome	+	−	−	−	−	−	−	+	−
Hypophosphatemic rickets	−	+	−	−	−	+	−	−	

[a] Clinical score according to Feuillan: ++ moderate form; +++ severe form.
C: cranial bones; LB: long bones.

treatment 9.6 y, range 5.7–14.6 y) were recruited from four Italian Departments of Paediatric Endocrinology from December 1993 to June 1998.

Diagnosis of MAS was made on the basis of clinical and hormonal examination, demonstrating, in association with BFD, skin dysplasia in eight, peripheral precocious puberty in all, adrenocortical nodular hyperplasia with ACTH-independent Cushing syndrome in two and hypophosphatemic rickets in two (Table 1). Two females with precocious puberty (patients 1 and 5) had been treated with testolactone (40 mg/kg/d) and underwent ovarian surgery before pamidronate therapy. Another (patient 3) continued testolactone treatment during pamidronate administration; the remaining four females and the two males (patients 8 and 9) were never treated due to the slow progression of precocious puberty. Cushing syndrome was treated in one little girl (patient 1) with oral ketoconazole (20 mg/kg/d) during the first year of life; clinical and hormonal signs of hypercortisolism progressively disappeared thereafter. In the other patient (patient 8), hypercortisolism disappeared spontaneously during the first year of life. On the basis of metabolic evaluation hypophosphatemic rickets was diagnosed in two patients (patients 2 and 6) and was treated with oral phosphates (3–4 g/d) during the whole study period.

BFD severity was graded according to Feuillan's score (18): mild (absence of facial asymmetry, limb length discrepancy or gait abnormality); moderate (obvious facial/skull asymmetry, limb length discrepancy, no fractures or corrective surgery); severe (as in moderate, but with fractures and/or need for surgical correction). All patients were affected by moderate or severe forms of BFD.

Pamidronate was started at 0.5 mg i.v./kg/d for 2 consecutive d at a 1-y interval (5 patients enrolled between 1993 and 1994, Table 2). Due to clinical improvement and lack of side effects the subsequent therapeutic cycles in all patients were instituted at 6 mo intervals at 1 mg i.v./kg/d for 3 consecutive d; total dosage over 3 d was limited to 180 mg. The number of therapeutic cycles varied from 2–5. The cumulative dose ranged from 4–12 mg/kg.

Before treatment, clinical, auxological, metabolic, densitometric, radiological and scintigraphic parameters were assessed. Clinical, auxological, metabolic and densitometric evaluations were repeated before each therapeutic cycle, and radiographic and/or scintigraphic imaging at 1-y intervals.

As for clinical manifestations, pain was rated on a scale from 0–9: 0 for no pain, 1–3 for low, 4–6 for moderate, 7–9 for severe. The number of spontaneous fractures was recorded, and gait abnormality, limb and skull deformities, visual and hearing loss were all clinically investigated. Height, weight, height velocity and bone age according to Tanner's standards (19) were assessed in all patients at 1-y intervals from the beginning of the study.

The following bone metabolism markers were evaluated on blood and urine samples, respectively: blood calcium, phosphates and alkaline phosphatase and urinary calcium, phosphates and hydroxyproline. Calcium, phosphates, alkaline phosphatase and hydroxyproline were assessed according to chemical methods. Reference values were obtained in a cohort of sex- and age-matched children.

Changes in bone mineral density of the lumbar spine were measured with DEXA Hologic QDR 1000 on L1–L4. Because bone mineral density (BMD) values increase with age in the normal population, BMD values were expressed as standard deviations (SD) of the mean (Z score) to compare BMD values of patients of different ages. Reference values were obtained in a cohort of age-, sex- and puberty-matched children.

Radiographs of the affected bones were taken with standard methods. The number and morphology of BFD sites were detected by ^{99}Tcm-labelled bisphosphonate scintigraphy. We carefully watched for side effects such as pain, fever and hypocalcemia during and at the end of pamidronate infusion. Possible metaphyseal lesions were investigated using a left wrist radiogram performed at 1-y intervals starting from the third pamidronate cycle.

Statistical analysis was performed using Wilcoxon's rank-sum test and linear regression and correlation.

Table 2. Variation in clinical signs of bone dysplasia with treatment.

	DPE	CM	NA	LR	CD	DRD	CA	MR	AR
Cases	1	2	3	4	5	6	7	8	9
Age of start (y)	5.7	5.9	6.7	6.9	9.9	11.2	13.1	12.7	14.6
Cycles (*n*)									
(0.5 mg/kg × 2 d)			2	1	2	1			1
1 mg/kg × 3 d	2	2	3	3	2	1	2	4	1
Cumulative dose (mg/kg)	6	6	11	10	8	4	6	12	4
Treatment (y)	1	0.5	3.5	2	3	1.5	0.5	1.5	1
Clinical score[a]									
At diagnosis	++	+++	+++	−++	−+	++	++	+++	++
At the end	++	++	+++	++	++	++	++	+++	++
Fractures (*n*)									
Before treatment	−	2	5	2	−	−	−	7	−
During treatment	−	−	−	−	−	−	−	−	−
Pain									
At diagnosis	−	+	+	+	−	+	−	+	+
At the end	−	−	−	−	−	−	−	+	−
Gait abnormality									
At diagnosis	−	+	+	+	−	+	−	+	−
At the end	−	+	+	−	−	−	−	+	−
Limb discrepancy									
At diagnosis	−	+	+	+	−	+	−	+	−
At the end	−	+	+	+	−	+	−	+	−
Cranial asymmetry									
At diagnosis	−	+	−	−	+	−	−	+	
At the end	−	+	−	−	+	−	+	+	

[a] According to Feuillan: ++ moderate form; −++ severe form.

Results

Clinical results of pamidronate treatment are reported in Table 2. At diagnosis in four patients (patients 2, 3, 4 and 8) BFD was scored as severe; in two (patients 2 and 4) it was reduced to moderate at the end of the study. In the subjects with severe BFD at diagnosis, spontaneous fractures occurred 1–3 y before treatment, ranging from 2–7 per patient (mean 1.8 fractures/patient/y). No further fractures occurred in these patients, nor in the subjects with moderate BFD, during treatment. Bone pain was detected and recorded in six patients (patients 2, 3, 4, 6, 8 and 9) at diagnosis (Fig. 1a): low pain (score 1–3) disappeared after the first therapeutic cycle, while moderate or severe pain (score 4–9) disappeared after the third cycle. A statistically significant decrease in pain (Wilcoxon's rank-sum test: $W = 21$; $p < 0.06$) occurred at the end of the first cycle.

With treatment, gait abnormality disappeared in two of five patients (patients 2, 3, 4, 6 and 8), while limb discrepancy (five cases: patients 2, 3, 4, 6 and 8) and cranial asymmetry (five cases: patients 2, 5, 7, 8 and 9) did not change.

Serum alkaline phosphatase (ALP) levels were elevated in all nine patients at the beginning of treatment (Fig. 1b): in four of them (patients 4, 5, 6 and 9) at upper normal limits, while in five (patients 1, 2, 3, 7 and 8) levels were clearly elevated (>1500 mU/ml). ALP decreased with treatment in all patients; in particular it was reduced to normal levels (<1000 mU/ml) after two cycles in patients 4, 5, 6 and 9 and after four cycles in patient 3. A statistically significant decrease in ALP (Wilcoxon's rank-sum test: $W = 45$; $p < 0.06$) was found at the end of the first therapeutic cycle.

Urinary hydroxyproline (OHP) levels (Fig. 1c) were elevated in all nine patients at the beginning of treatment: in four of them (patients 1, 4, 5 and 6) at upper normal limits, while in five (patients 2, 3, 7, 8 and 9) levels were clearly elevated (>100 mg/g creatinine). With treatment a statistical significant decrease was found at the end of the first therapeutic cycle (Wilcoxon's rank-sum test: $W = 26$; $p < 0.06$).

A positive significant correlation (linear regression: $r = 0.7$, $p < 0.05$) was found between ALP and OHP levels in basal conditions.

Pretreatment serum and urine calcium levels were normal, while transient hypocalcemia was seen during pamidronate infusion in four patients (patients 2, 3, 6 and 8). Serum pretreatment phosphate levels were reduced (<0.96 mmol/l) in two patients whose phosphate urinary excretion was enhanced (>20 mmol/l). In these two patients and in the others, phosphate levels did not change significantly during pamidronate treatment.

Bone mineral densitometric values (BMD) were low at diagnosis (between −1 and −2.5 SDS) in four patients (patients 3, 5, 8 and 9) and increased to normal with treatment (Fig. 1d). A statistically significant increment in BMD values (Wilcoxon's rank-sum test: $W = -28$; $p < 0.06$) was found at the end of the first therapeutic cycle.

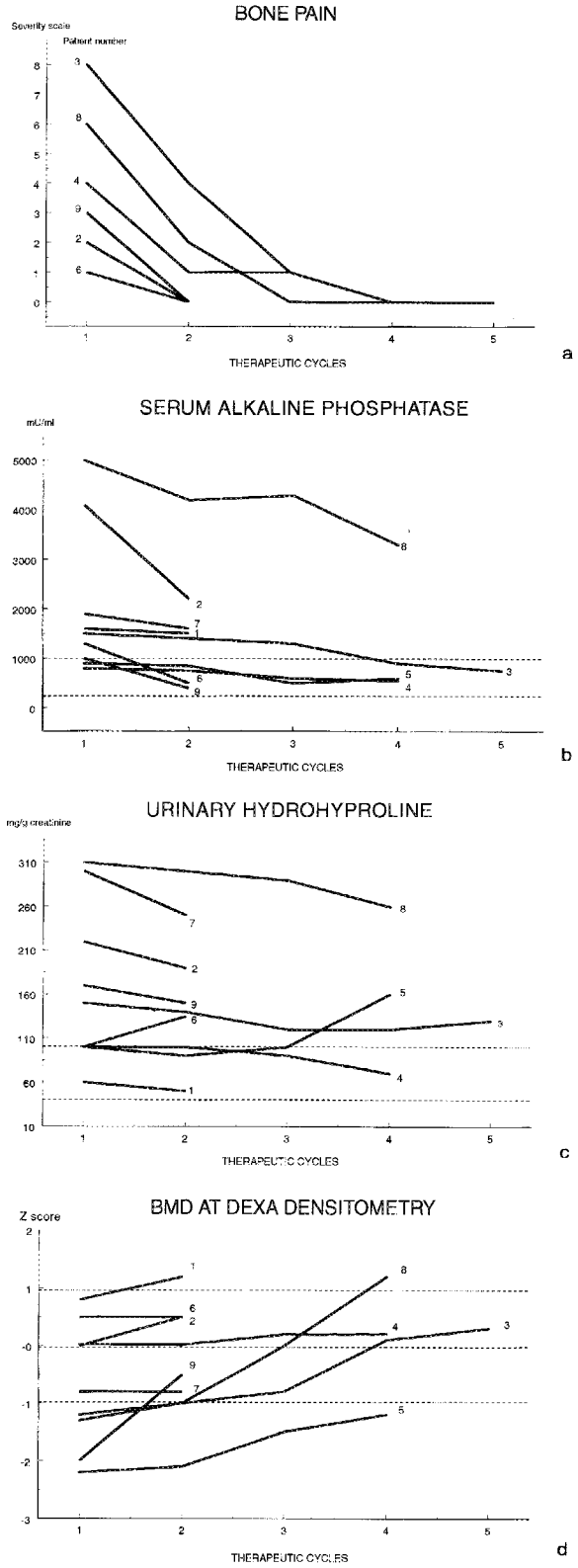

Fig. 1. Effects of pamidronate treatment on (a) bone pain, (b) serum alkaline phosphatase, (c) urinary hydroxyproline and (d) bone mineral density. Dotted lines: range of reference values.

Scintigraphy was carried out more than once in seven of nine cases, showing an increase in number and extension of the lesions in four (patients 2, 3, 5 and 6), stability in lesion number and extension and in intensity of ^{99}Tcm uptake in two (patients 8 and 9) and reduced uptake in one (patient 4).

X-rays did not clearly demonstrate signs of lesion healing.

Only a few light side effects were seen: five patients had transient pain of the affected bones, mainly during the first pamidronate infusion, in some instances with fever, easily treated with analgesic-antipyretic drugs. Transient hypocalcemia (175–210 mmol/l) was documented at the end of some infusions. It did not cause clinical signs or symptoms and disappeared within a few hours.

Left wrist radiograms showed normal progression of bone age and radiolucent transversal lines at metaphyseal levels, which appeared after each therapeutic course and did not affect bone growth or morphology. During treatment, height Z score values (Fig. 2) did not change significantly, and height velocity was normal (+1 to −1 SDS) in all patients. Neither gastric pain nor phlebitis was observed.

Discussion

The pathogenesis of BFD in MAS has only recently been elucidated. It consists of hyperproliferation of mutated pre-osteoblastic cells, which substitute the normal bone trabeculae with woven bone and fibrous tissue of specific histologic appearance in the appendicular-axial bones on one side, and in facial and skull bones on the other (6). The hyperactivation of pre-osteoblastic cells causes hyperactivity of osteoclasts through local humoral signals such as interleukin-6 (20). Indeed, osteoclastic cells have been found on the border of typical fibrous dysplasia lesions (21).

The therapeutic option of pamidronate, an anti-osteoclastic agent employed effectively in Paget disease (22), can also be considered in MAS BFD. Until now, the little data there are on bisphosphonate treatment have been almost exclusively obtained in adults with isolated BFD (12–15). In MAS, particularly in children, only one preliminary report exists with favourable results in clinical and biochemical terms (17).

Bone involvement in our patients caused physical handicaps such as abnormal body proportions, progressive facial disfiguring, recurrent fractures and pain.

This was an open study, not controlled or randomized. Notwithstanding this, its preliminary results indicate that pamidronate is effective from the first cycle, in accordance with the results of Glorieux (17), in reducing fractures and pain and, as a consequence, gait abnormality. Abnormal body proportions were unchanged, but no clear disease progression was seen. The importance of reducing fracture rates in these

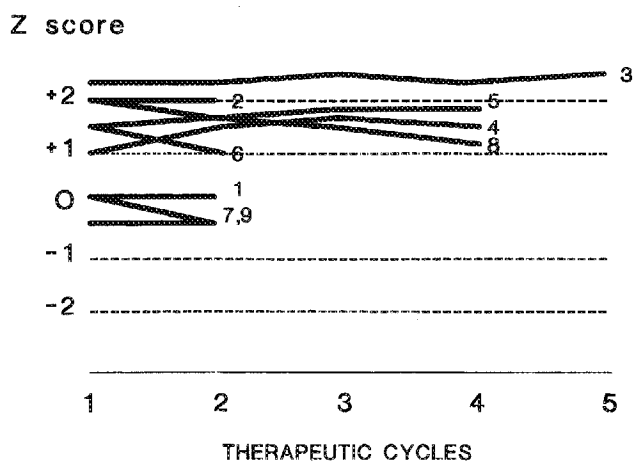

Fig. 2. Height during pamidronate treatment.

patients, thus minimizing their need for orthopaedic reconstructive surgery, must be stressed. If surgery is unavoidable, at least a better quality of bone should be expected.

In addition, pamidronate can normalize the reduced mineral content of the unaffected bones, enhancing skeletal resistance to mechanical load.

The rise of ALP and OHP levels demonstrates enhanced bone turnover. The positive correlation between ALP and OHP before treatment indicates higher osteoclastic activity in patients with higher pre-osteoblastic activity. On the other hand, no correlation between BFD clinical score and bone markers could be found, confirming the clinical and metabolic heterogeneity of BFD. ALP and OHP were progressively reduced by the treatment in all patients, although normal values were attained only in those with upper normal pre-treatment values. This effect of pamidronate in reducing osteoclastic and osteoblastic activity markers demonstrates its efficacy at the lesional level in MAS patients.

Radiological and scintigraphic evidence of healing was not found, in contrast with the data in adults (12–15), probably because of the shortness of the therapeutic course, the disease severity and the specific dynamics of bone growth in paediatric patients.

Treatment caused only minor side effects such as short-term hypocalcemia, pain and fever, while significant metaphyseal alterations and reduction of linear growth were not observed.

These preliminary data indicate that pamidronate can be considered as a therapeutic option in children and adolescents with moderate or severe BFD in McCune-Albright syndrome, since it reduces pain and fractures and ameliorates bone strength both at the lesional and non-lesional levels, with few short- or long-term side effects. Although radiological evidence of healing was not obtained, disease stability can still be seen as a therapeutic result in children and adolescents with severe and progressive BFD. Larger controlled trials are needed to confirm these preliminary data.

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